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| EXAMINER | |
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| WANG, CHANG YU | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/806,611 | COLLINS ET AL. | |
| | Examiner | Art Unit | |
| | Chang-Yu Wang | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on 5/18/07.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-49 is/are pending in the application.

4a) Of the above claim(s) 20-28 and 41-49 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19 and 29-40 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) 1-49 are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 5/18/07.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

## RESPONSE TO AMENDMENT

### *Status of Application/Amendments/claims*

1. Applicant's amendment filed May 18, 2007 is acknowledged. Claims 1-49 are pending in this application. Claims 20-28, and 41-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

2. Claims 1-19, 29-40 are under examination in light of IFN-1α/β in this office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

4. Applicant's arguments filed on May 18, 2007 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

### *Claim Rejections/Objections Maintained*

### *Claim Rejections - 35 USC § 112*

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 29-40 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing production of IL-10 and decreasing INF-γ IL-1α, IL-2, IL-6, IL-18 and increasing T cell proliferation in an EAE animal model by administration of the IL-21 polypeptide of SEQ ID NO:2 to decrease the severity of

symptoms that are regulated by inappropriate cytokine production, does not reasonably provide enablement for treating, preventing or ameliorating multiple sclerosis associated with an IL-10 deficiency, increased IFN-g, increased IL-1a, increased IL-2, increased IL-6 or increased IL-18 or other disorders associated with an IL-10 deficiency by administering to a subject any unknown agonist of IL-21/IL-21R as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is maintained for the reasons made of record in Paper No.20061003 and as follows.

Applicant describes an increase of T cell proliferation and IL-10 production and a decrease IFN-γ by mouse oligodendrocyte glycoprotein (MOG) 35-55 peptides in cells derived from lymph nodes in vitro. Applicant also describes reduction of the severity of an EAE animal model induced by PLP139-151 plus petussis toxin (one of the animal models for multiple sclerosis) by SEQ ID NO:2 (the IL-21 polypeptide). Applicant further shows that IL-10 is upregulated and IFN-γ and IL-1α, IL-2, IL-6 and IL-18 are downregulated in the EAE animal model.

Applicants argue that the claimed agonistic anti-IL-21R antibodies do not encompassing antagonistic anti-IL-21R antibodies and they are enabled for treating, preventing or ameliorating MS or a symptom as recited in amended claims (p. 18-20 of the response). Applicants argue that the claims recite agonistic IL-21 polypeptide with at least 90% identity to SEQ ID NO:2 and the specification provides sufficient guidance as to how to make these claimed polypeptides that can be used in the claimed methods (p.

20-22 of the response). Applicants argue that the data derived from the EAE animal model is sufficient to support the claimed methods of treating, preventing, or ameliorating MS or a symptom as recited in the claims or other disorders associated with an IL-10 deficiency and cites In re Brana and Steinman et al. (Ann Neurol. 2006. 60: 12-21) (p. 23-25 of the response). Applicants argue that the method of preventing MS by evaluation of an IL-10 parameter is enabled because MS is associated with an IL-10 deficiency (p. 27 of the response). Applicants' arguments have been fully considered but they are not persuasive.

In contrast to Applicants' assertion on p. 18-20 with respect to the enablement of agonistic anti-IL-21 antibodies that are used in the claimed methods, it is noted that although generation of an antibody is routine in the art, an antibody with agonistic activity does require the knowledge of what specific epitopes are required for binding of an agonistic antibody to IL-21R and subsequently activating IL-21R. To determine whether the disclosure is enabling is based on the guidance on how to make and use rather than how to screen.

In addition, the claims not only encompass the whole molecule of an agonistic anti-IL-21 antibody but also include an antigen-binding fragment of the antibody. The specification fails to provide sufficient guidance as to how to make and use a specific agonistic anti-IL-21 antibody and its antigen-binding fragments as recited in the claims since no defined structure and no specific amino acid sequences required for making these specific agonistic antibodies and antigen-binding fragments are recited in the claims. The specification does not limit the definition of "IL-21/IL-21R" to such a closed-

ended definition. In other words, this definition does not state, nor limit IL-21/IL-21R polypeptides that comprise peptides of different epitopes, which are further not defined or recited within the claims. Therefore, as previously made of record, because no specific epitopes, no specific base amino acid sequence are recited in the current claims and no guidance is provided in the specification as to what minimal structural requirements are required for making agonistic antibodies or fragments, which containing "variant" epitopes, the skilled artisan would not know how to make and use the instant invention, as currently claimed, without requiring undue experimentation.

Accordingly, the court in *Genentech, Inc., v. Novo Nordisk*, 42 USPQ2d 1001, 1005 (1997), held that "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable", and that "reasonable detail must be provided in order to enable members of the public to understand and carry out the invention".

In contrast to Applicants' assertion on p. 20-22, the specification does not limit the definition of "an IL-21 polypeptide" to such a closed-ended definition, as discussed above. The specification fails to provide sufficient guidance as to how to make and use a functional IL-21 polypeptide having at least 90% identity to SEQ ID NO:2. As previously made of record, a single amino acid change would abolish a ligand binding to its receptor. The specification fails to teach what specific amino acid sequences need to be conserved and what amino acid could/could not tolerate modification. Although the specification outlines art-recognized procedures for producing and the screening method, this is not adequate guidance as to the nature of active agonistic IL-21 polypeptides that must be constructed, and therefore is merely an invitation to use the current invention as a starting point for further experimentation.

In response to Applicants' arguments with regard to enablement of treating, preventing, ameliorating MS or a symptom or other disorders (p. 23-25 of the response), the specification fails to provide sufficient guidance as to enable one of skill in the art to practice the fully scope of the invention. Based on the specification and prior art, Applicant is enabled for increasing T-cell proliferation and IL-10 production and decreasing IFN-γ and IL-1α, IL-2, IL-6 and IL-18 in vitro or in an EAE animal model. However, the claims are not limited as set forth above because the claims as amended are directed to methods of treating, preventing or ameliorating a disease using an agonist of IL-21/IL-21R. The specification defines the claimed methods as encompassing

"a method of treating (e.g., curing, suppressing, ameliorating, reducing, or delaying) or preventing (e.g., preventing the onset of, or preventing recurrence or relapse of) an immunological disorder of the nervous system (e.g., a chronic immunological disorder of the nervous system, including multiple sclerosis" (see p. 3, [007]; p.35 [0125]).

Neither the specification nor the prior teaches curing MS or a symptom or other disorder by any agonist of IL-21/IL-21R. Importantly, the claims encompass prevention of a disease. Currently there is no cure for MS. For example MS or other immunological disorders may be also due to genetic mutation, which is a natural process that cannot be prevented. Accordingly, the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity is unpredictable and the experimentation left to those skilled in the art is extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the

skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation.

In contrast to Applicants' assertion on p. 27 with regard to preventing MS by evaluating an IL-10 parameter, the specification describes several diseases that are associated with an IL-10 deficiency, indicating that evaluation of an IL-10 parameter is not indicative of MS. In addition, the claims recite an IL-10 parameter. However, the specification only describes the expression level or activity of IL-10 without further limiting what specific activity can be considered as an IL-10 parameter. Thus, a skilled artisan would not know what to measure or how to evaluate an IL-10 parameter and further determine whether an undefined IL-10 parameter can then be an indicator of the status of MS or other diseases. Accordingly, the rejection of claims 1-19, 29-40 under 35 U.S.C. §112, first paragraph, because the specification does not enable the invention commensurate in scope with claims is maintained.

6. Claims 1-3, 29-30, 34-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons made of record in Paper No.20061003 and as follows.

Applicants argue that the claims meet the written description requirement because Applicants are in possession of the genus of IL-21 polypeptides with at least

90% identity and the specification shows human and mouse IL-21 polypeptides that share 61% identity and cites Brandt et al. (J. Leukoc. Biol. 2001 (suppl) 46 (abstract. 119). Applicants' arguments have been fully considered but they are not persuasive.

As previously made of record, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, *as of the filing date sought*, he or she was in possession *of the claimed invention*". "The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* [emphasis added]". Therefore, Applicants' arguments are not persuasive.

In contrast, an invitation for others to discover a representative number of species, or to discover what constitutes any particular portion of the structure that must be conserved, with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics has not reasonably been provided within the instant specification. Thus, the specification fails to demonstrate possession of the genus of agonist of IL-21/IL-21, the genus of IL-21 polypeptides with at least 90% identity and the genus of antigen-binding fragments that can be used in the claimed method.

Accordingly, the court held in *Univ. California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) that:

"One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is", and also See *In re* Angstadt, 537 F.2d at 502-03, 190 USPQ at 218".

Thus, Applicants were not reasonably in possession of the "claimed genus of agonist of IL-21/IL-21, the genus of IL-21 polypeptides with at least 90% identity and the genus of antigen-binding fragments" that could be used in the claimed method, and for the reasons previously made of record. See again MPEP 2163. Therefore, the rejection of claims 1-3, 29-30, 34-40 under 35 U.S.C.§ 112, first paragraph, for failing to meet the written description is maintained.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-19 and 34-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is maintained for the reasons made of record in Paper No.20061003, and as follows.

Applicants argue that IL-10 activity is not definite because IL-10 activity is known in the art and the specification teaches regulating MS symptoms (p. 33 of the response). Applicants' arguments have been fully considered but they are not persuasive.

In response, although different activities for IL-10 have been shown in the art, it is not clear what specific activity of IL-10 can be determined and to be used in the claimed method since the claims do not limit a specific activity and there are many different activities of IL-10. Although Applicants describe several assays to evaluate IL-10 activity in the art, Applicants fail to limit what specific parameter and activity of IL-10 are and thus would be included in the limitation of the claims. The disclosure also fails to set

forth the metes and bounds of what is encompassed within the definition of "an IL-10 parameter". Thus the artisan would not know what responses Applicant intended to measure. Accordingly, the rejection of claims 16-19 and 34-40 under 35 U.S.C. 112, second paragraph, for being indefinite is maintained.

***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 9-12, 14, 29-34 stand rejected under 35 U.S.C. 102 (e) as being anticipated by Novak et al. (US Patent No. 6605272, issued Aug 12, 2003, priority date Mar 9, 1999, as cited in IDS submitted May 23,2006). The rejection is maintained for the reasons made of record in Paper No.20061003 and as follows.

Applicant argues that Novak (US'272) does not teach the claimed method by using IL-21 (ZALPHA11 ligand disclosed in Novak (US'272)) because Novak (US'272) only teaches IL-21 mediates its effects through B cells and NK cells and MS is a T-helper1-driven autoimmune disease (p.35 of the response). Applicant argues that Novak (US'272) does not teach all the limitations of claims 1-4, 9-12, 14, 29-34, which currently amended as treating, preventing or ameliorating MS or a MS symptom

associated with an IL-10 deficiency, increased IF-γ, IL-1α, IL-2, IL-6 or IL-8 and does not teach how to use IL-21 in treating MS (p. 36 of the response). Applicants' arguments have been fully considered but they are persuasive.

In contrast to Applicants' assertion on p. 35 of the response, Novak (US'272) does teach a therapeutic use of IL-21 (ZALPHA11 ligand) in several immunological disorders including multiple sclerosis (i.e. as it relates to claims 1-4, 9-12 and claims 29-34; see col. 42, lines 9-31; col.192-198, claims 1-21). In addition, in response to Applicants' argument that Novak (US'272) does not teach regulation of T cells and cytokines, Applicants are incorrect. Novak (US'272) does teach that IL-21 enhances proliferation of $CD4^+$ T cells, $CD8^+$ cytotoxicity T cells and Natural killer cells and regulating production of cytokines such as increasing IL-10 decreasing IFN-γ to treat immunological disorders mediated by cellular immunity (i.e. as it relates to claims 1, 29, 34; see col.99-102, examples 41-42). The limitation of ameliorating a symptom of MS or MS associated with an IL-10 deficiency or disorders caused by inappropriate production of cytokines would be an inherent result of regulating immune responses of T cell proliferation and cytokines productions by administration of IL-21 (i.e. as it relates to claims 1-4, 9-12, 29-31 and 34, which is an agonist of the IL-21 receptor by definitation) because Novak teaches the same step of administration of IL-21 as claimed. As previously made of record, enhancing secretion of IL-10 and decreasing IFN-γ by IL-21 are evidenced by Wurster et al.. Novak (US'272) also teaches an intravenous administration route and doses (i.e. as it relates to claims 10-12 and 14; see col.95, lines 40-55; table 6). Novak (US'272) further teaches preparing a recombinant IL-21

polypeptide from mammalian cells and *E. coli* cells (i.e. as it relates to claims 32 and 33; see col. 109, example 46; col.80-86, Examples 30-31). Therefore, the rejection of claims 1-4, 9-12, 14 and 29-34 under 35 U.S.C. 102 (e) as being anticipated by Novak et al. (US Patent No. 6605272) is maintained.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 29-34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Novak et al. (US Patent No. 6605272, issued Aug 12, 2003, priority date Mar 9, 1999, as cited in IDS submitted May 23,2006) in view of Carter et al. (US20030108549A, published Jun 12, 2003, priority date Oct 4, 2001) and Kawai et al. (Cell Immunol. 1996. 171:262-8). The rejection is maintained for the reasons made of record in Paper No.20061003 and as follows.

Applicants argue that Novak (US'272) does not meet all the limitations of the claims because it does not teach treating, preventing or ameliorating MS or a symptom of MS associated with an IL-10 deficiency, increased IF-γ, IL-1α, IL-2, IL-6, or IL-18. Applicants argue that Carter (US'549) and Kawai et al. do not overcome the deficiency of Novak (US'272) because Carter (US'549) teaches using an IL-21 antagonist to treat MS and Kawai et al. only teach intracerebroventricular and intrathecal administration without treating MS or a symptom recited in the amended claims (p. 39 of the response). Applicants' arguments have been fully considered but they are not persuasive.

In contrast to Applicants' assertion, Novak (US'272) does teach the limitation of the claims 1-4, 9-12, 14 and 29-34 as set forth in Paper No. 20061003 and paragraph 8. Although Novak (US'272) does not teach an agonistic anti-IL-21 antibody (i.e. as it relates to claims 5-6), Carter (US'549) teaches an agonistic anti-IL-21R antibody (as it relates to claims 5-6; see p. 3 [0023], p.5 [0041]). Although Novak (US'272) does not teach an anti-inflammatory agent (i.e. as it relates to claims 7-8), Carter (US'549) teaches using a combination of anti-inflammatory agent including IFN-1α/β and an IL-21/IL21R agonist to treat T cell-mediated diseases such as tumor (i.e. as it relates claims 7-8; see p.3 [0024], p.5 [0039], [0040], [0208]). Carter (US'549) also teaches that an IL-21/IL21R agonist enhances T cell proliferation and cytokine regulation, which relates to ameliorating a symptom of MS or disorders-associated with cytokines (as it relates to claims 1, 29 and 35; see [0327], Examples 9-11).

In contrast to Applicants' assertion that Carter (US'549) teaches using IL-21

antagonists to treat MS on p.39 of the response, Applicants are incorrect. It is noted that the diseases described in Carter (US'549) is a general list to be treated using IL-21 agonists and antagonists. The IL-21 agonists are also described as to enhance immune responses and to treat autoimmune diseases, which includes MS. In addition, although Novak (US'272) and Carter (US'549) do not teach injection of IL-21 agonists into the CNS (i.e. as it relates to claims 13-15), Kawai et al. teach administering monoclonal antibodies that are against LFA-1 and ICAM-1 in EAE rat model by intracerebroventricular and intrathecal administration routes (i.e. as it relates to claims 13-15; see p. 262, abstract and p. 263 materials and methods). Administration of agents (IL21 agonists) to the cerebrospinal fluid (CSF) as in claim 15 is an intrinsic result of intrathecal or intracerebroventricular administration because of the nature of neuroanatomy, which means that drugs administered by injection actually means injected to the CSF by definition.

Thus, the claimed methods are obvious over the applied references because a composition comprising an anti-inflammatory agent and IL-21 or an agonistic anti-IL-21R antibody has been successfully used to enhance immune responses of T cell proliferation and cytokine regulation, which would subsequently result in ameliorating a symptom of MS or MS associated with IL-10 deficiency or disorders caused by inappropriate production of IL-10 and IFN-$\gamma$. In addition, it would also have been obvious to one of ordinary skill in the art at the time the instant invention was made to treat MS or ameliorate a symptom of MS by intracerebroventricularly and/or intrathecally administering to the central nervous system or into CSF a composition comprising an

anti-inflammatory agent and an agonist of IL-21/IL21R including the IL-21 polypeptide of SEQ ID NO:2 and an agonist anti-IL21R antibody since intracerebroventricular and intrathecal administration of monoclonal antibodies of LFA-1 and ICAM-1 to an EAE animal model (a MS model) successfully reduces the severity of the animal model and IL-21 can be used to treat MS.

10. Claims 1-19, 29-40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Novak et al. (US Patent No. 6605272, issued Aug 12, 2003, priority date Mar 9, 1999, as cited in IDS submitted May 23,2006), Carter et al. (US20030108549A, published Jun 12, 2003, priority date Oct 4, 2001) and Kawai et al. (Cell Immunol. 1996. 171:262-8) as applied in claims 1-15, 29-34 above and further in view of Beebe et al. (Cytokine & Growth Factor Rev. 2002. 13: 403-12 as in IDS submitted on 05/23/06). The rejection is maintained for the reasons made of record in Paper No.20061003 and as follows.

Applicants argue that although Beebe teaches an association of increased IL-10 with the treatment of MS, Beebe does not provide any association between IL-21 agonists and IL-10 levels. Applicants argue that the combination of applied references of Novak (US'272), Carter (US'549), Kawai and Beebe does not teach the claimed methods and the nexus between IL-21 and IL-10 (p. 42 of the response). Applicants' arguments have been fully considered but they are not persuasive.

In contrast to Applicants' assertion, the claimed methods are obvious over the applied references. As previously made of record, Novak (US'272) teaches a

therapeutic use of IL-21 (ZALPHA11 ligand) in several immunological disorders including multiple sclerosis (i.e. as it relates to claims 1-4, 9-12, 14 and 29-34), Carter (US'549) teaches enhancement of T cell proliferation and cytokine regulation by an IL-21/IL21R agonist including an agonist anti-IL-21R and a composition comprising an anti-inflammatory agent and an IL-21/IL-21R agonist (i.e. as it relates to claims 5-8), Kawai teaches intracerebroventricular and intrathecal administration of monoclonal antibodies in a MS animal model (as it relates to claims13-15) and Beebe teaches that the level of IL-10 is low in MS patient but the level is increased after treatment of the disease (as it relates to claims 16-19 and 34-40). The teachings of Beebe provide a motivation and expectation of success in evaluating the level of IL-10 in MS patients before and after treatment.

Thus, it would have been obvious for one of ordinary skill in the art to be motivated and have expected success in ameliorating a symptom of MS regulated by inappropriate production of IL-10 and IFN-γ by incorporating the teachings of Beebe et al. to measure/monitor the levels of IL-10 in MS patients while treating patients with IL-21 agonists/ agonist anti-IL-21R antibodies since a low level of IL-10 is found in MS and EAE, and the level of IL-10 increases after a successful treatment of MS patients. Accordingly, the rejection of claims 1-19, 29-40 for being unpatentable over Novak et al. (US'272), Carter et al. (US'549A), Kawai et al. and Beebe et al. is maintained.

***New Grounds of Rejection***

***Claim Rejections - 35 USC § 112***

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 and 29-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims as amended are directed to a method of treating, preventing or ameliorating a symptom of multiple sclerosis associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6 or increased IL-18 in a subject by administration of an agonist of an IL-21/IL-21R wherein the agonist is selected from an IL-21 polypeptide, an agonistic anti-IL-21R antibody and an antigen-binding fragment of an agonistic anti-IL-21R antibody. The instant claims now recite limitations of "multiple sclerosis associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6 or increased IL-18", which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant fails to disclose multiple sclerosis associated with increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6 or increased IL-18 as recited in claims 1 and 29. The specification fails to disclose the limitation of multiple sclerosis associated with increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6 or increased IL-18. Applicant only discloses "disorders that can be associated with an IL-10 deficiency include multiple sclerosis, significant inflammatory events (including ischemia-reperfusion injury), psoriasis and pemphingus" (see p. 8, [0026] of the specification). Support is not found for multiple sclerosis associated with increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6 or increased IL-18 as disclosed in the original specification and thus the recitations constitute new matter absent evidence for their support. Applicant is invited to clearly point out the written support for the instant limitations.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 and 29-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-19 and 29-40 are indefinite because Applicants recite "a symptom of multiple sclerosis associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6 or increased IL-18". Applicant only describes "general symptoms of MS include tremor, poor coordination, difficulty walking, and other problems" on p. 3 of the specification but fails to

define/describe what is encompassed within "a symptom of multiple sclerosis associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6 or increased IL-18". The disclosure fails to set for the metes and bounds of what is encompassed within the definition of such a symptom of multiple sclerosis associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6 or increased IL-18; and thus the claims are indefinite.

***Conclusion***

13. NO CLAIM IS ALLOWED.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
July 18, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER